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I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003906842 for a patent by ACRUX DDS PTY. LTD. as filed on 10 December 2003.

WITNESS my hand this
Twenty-fourth day of December 2004

A handwritten signature in black ink, appearing to read "J. K. Peisker".

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES



AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: METHOD OF TREATMENT FOR UNDESIRED
EFFECT FOLLOWING TRANSDERMAL OR
TOPICAL DRUG DELIVERY

Applicant: **ACRUX DDS PTY LTD**

The invention is described in the following statement:

METHOD OF TREATMENT FOR UNDESIRED EFFECT FOLLOWING TRANSDERMAL OR TOPICAL DRUG DELIVERY

Field

5 The present invention relates to a composition and method for reducing the effective transdermal dose of a topically applied drug for treatment or prophylaxis of undesired effects. The method the invention provides a method for inhibiting the release of a drug in to the systemic circulation in circumstances such as an overdose or where an adverse reaction is desired or expected after
10 application.

Background

All drugs have the potential to be misused, whether legally prescribed by a doctor, purchased over-the-counter at the local drug store, or purchased
15 illegally. Taken in combination with other drugs or with alcohol, even drugs normally considered safe can cause death or serious long term consequences. Accidental drug overdose may be the result of misuse of prescription medicines or commonly used medications like pain relievers and cold remedies. Symptoms differ depending on the drug taken.

20 While many victims of undesired drug effects recover without long term effects, there can be serious consequences. Some drug overdoses may cause the failure of major organs like the kidneys or liver, or failure of whole systems like the respiratory or circulatory systems.

25 Drugs have effects on the entire body. Generally, in an overdose, the effects of the drug may be a heightened level of the therapeutic effects seen with regular use. In overdose, side effects become more pronounced, and other effects can take place, which would not occur otherwise. Large overdoses of some
30 medications cause only minimal effects, while smaller overdoses of other medications can cause severe effects, possibly death. Some overdoses may make worse a person's chronic disease. For example, an asthma attack or chest pains may be triggered.

Conventional means for administering antidotal agents to a human or animal suffering an undesired effect are to pump the stomach, thus mechanically remove unabsorbed drugs from the stomach, or to administer substances such as activated charcoal, to help bind drugs and reduce the amount absorbed into the blood. However, these methods are only applicable to treatment of oral overdose.

Administration of therapeutic agents through the skin ('transdermal drug delivery') has received increased attention because it is considered to not only provide a relatively simple dosage regime but also provide a relatively slow and controlled route for release of an agent into the systemic circulation. Thus, any adverse reaction or application error was traditionally remedied by removal of the transdermal system. However, with the current transdermal technology, the rate of transdermal uptake has dramatically increased, and risk of application error amplified along with it. Treatment of non-oral overdose currently requires administration of other medicines to reverse the effects or to prevent more harm.

Removal of drugs from the skin and/or systemic system offers several inherent clinical and patient advantages over the traditional remedies in that it is non-invasive, avoids further metabolism thus reducing the impact on the kidneys or liver, and can be self administered.

Structurally, the skin consists of two principle parts, a relatively thin outermost layer (the 'epidermis') and a thicker inner region (the 'dermis'). The outermost layer of the epidermis (the 'stratum corneum') consists of flattened dead cells which are filled with keratin. The region between the flattened dead cells of the stratum corneum is filled with lipids which form lamellar phases that are responsible for the natural barrier properties of the skin. Epidermal thickness is remarkably constant over the body, except on the soles of the feet and the palms of the hand (Rushmer, et al., 1966, *The Skin. Science* 154(3747), 343-348).

For effective transdermal delivery of a therapeutic agent that is applied to the surface of the skin ('topical application'), the agent must be partitioned firstly from the vehicle into the stratum corneum, it must typically then be diffused within the stratum corneum before being partitioned from the stratum corneum to the viable epidermis and dermis and then into the bloodstream. Many transdermal systems now available rely on the rapid uptake into the stratum corneum and subsequent partitioning, thereby creating a reservoir of drug within the skin. Whilst the patch or transdermal system may be removed, the drug reservoir remains and will continue to partition into the systemic circulation.

10

There is a need for simple, effective removal of drugs from the skin and/or systemic circulation to reduce or avoid an undesirable effect.

Summary

15 The present invention arises from the inventor's studies of transdermal and topical formulations which contain penetration enhancers that enhance the percutaneous absorption of a physiologically active agent. The inventor's studies have shown that the release of physiologically active agent may be inhibited to ameliorate an undesired effect such as caused by overdose or 20 adverse reaction.

The present invention provides a method for inhibiting the percutaneous absorption of a physiologically active agent topically applied to a transdermal administration site, the method including the step of applying a membrane, 25 coated with a layer of an adhesive, to the transdermal application site. The invention generally results in the treated subject receiving a serum concentration of topically applied drug which is less than would otherwise be provided. The membrane is preferably an occlusive or semi-permeable membrane.

30

According to the method of the invention the membrane may be applied to the transdermal administration site to achieve a reduction in the drug serum profile of the animal to reduce or prevent the occurrence of undesired effects of the transdermal drug delivery. The membrane is preferably applied to the whole of

the transdermal drug application site and more preferably will include the surrounding area. In this way it is possible to inhibit the increase in the blood serum profile. Indeed in some cases we believe that the method of the invention leads to the drug being extracted from the skin to significantly reduce both the increase in blood level and the total dose of drug which would otherwise be administered. Moreover in many cases these effects of reduced blood level and total dosage occur even when the membrane is applied after a significant period has elapsed since the topical application of the drug.

5

10 The present invention also provides a method for removal of physiologically active agent from the drug reservoir within the skin, the method including the step of applying a membrane to the transdermal drug administration site to reduce or eliminate the occurrence of undesired effect, wherein application of the membrane to the transdermal drug application site is used to extract the

15 physiologically active agent from the drug reservoir within the skin.

The invention further provides the use of an adhesive in preparation of a membrane composite for treatment or prophylaxis of the effects of transdermal administration of a drug.

20 Conveniently, the membrane is coated with a layer of an adhesive on the skin contacting side of the membrane, which holds the membrane in place and prevents surface wrinkling. Preferably the membrane and adhesive are pliable and move with the body. Preferably the membrane is transparent and the free

25 side of the membrane (that is the side remote from the side applied to the body) is resistant to liquids, thus enabling the individual to shower or bathe.

Detailed Description

Before describing the present invention in detail, it is to be understood that this

30 invention is not limited to specific drug delivery systems, device structures, enhancers or carriers, as such may vary. It is also to be understood that the terminology used is for the purpose of describing particular embodiments only, and is not intended to be limiting.

In describing the present invention, the following terminology will be used in accordance with the definitions set out below.

5 The terms "topical" and "transdermal" are used herein in the broadest sense to refer to administration of a drug to the skin surface or mucosal membrane of an animal, including humans, so that the drug passes through the skin tissue and/or into the animal's blood stream, thereby providing a local or systemic effect. The term transdermal is intended to include transmucosal drug 10 administration i.e. administration of a drug to the mucosal surface of an animal so that the drug passes through the mucosal tissue and into the blood stream. Unless otherwise stated or implied, the terms topical drug delivery and transdermal drug delivery are used interchangeably.

15 The term "skin-reservoir" is used herein in its broadest sense to refer to a depot or deposit of active agent and dermal penetration enhancer within the epidermis, whether it is intra-cellular (within keratinocytes) or inter-cellular.

20 The term "stratum corneum" is used herein in its broadest sense to refer to the outer layer of the skin, which is comprised of (approximately 15) layers of terminally differentiated keratinocytes made primarily of the proteinaceous material keratin arranged in a 'brick and mortar' fashion with the mortar being comprised of a lipid matrix made primarily from cholesterol, ceramides and long chain fatty acids. The stratum corneum creates the rate-limiting barrier for 25 diffusion of the active agent across the skin.

30 As mentioned previously, the present invention provides a method for reducing or eliminating the percutaneous absorption of a physiologically active agent thereby preventing elevated drug serum concentrations within the bloodstream of an animal suffering from an undesired effect of a transdermally administered drug, the method including the step of applying an occlusive or semi-permeable membrane, coated with a layer of an adhesive, to the transdermal application site.

Typically, the membrane will comprise of a suitable elastic, occlusive or semi-permeable layer such as films of polyurethane and ethyl vinyl acetate copolymers, hydrocolloid or cellulose.

5 Conveniently, the membrane of the current invention comprises an adhesive layer on one side. The adhesive layer will be comprised of a material that is permeable to the drug intended to be extracted. Examples of suitable materials for the adhesive layer include acrylics, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene vinyl acetate copolymers, tacky rubbers such as polyisobutene and the like.

10

The membrane will typically be less than 5 mm thick, more preferably less than 2 mm thick.

15 A benefit of the method of the present invention is that, in the event of an undesired effect, the systemic or local uptake may be prevented or reduced, thereby reducing or eliminating the effect and potential side effects. In contrast with other overdose treatments, the method of the present invention can be self administered safely, quickly and efficiently without encountering the gastro 20 irritation problems of traditional remedies.

25 The method of the present invention may be applied to inhibit or reduce any transdermal or topical delivery system comprising a physiologically active agent which can be delivered through the skin with or without the assistance of a dermal penetration enhancer. A list of suitable physiologically active agents includes, but is not limited to:

Antidiarrhoeals such as diphenoxylate, loperamide and hyoscyamine.

30 Antihypertensives such as hydralazine, minoxidil, captopril, enalapril, clonidine, prazosin, debrisoquine, diazoxide, guanethidine, methyldopa, reserpine, trimetaphan and lacidipine.

Calcium channel blockers such as diltiazem, felodipine, amlodipine, nitrendipine, nifedipine and verapamil.

Antiarrhythmics such as amiodarone, flecainide, disopyramide, procainamide, 5 mexiletene and quinidine.

Anti-angina agents such as glyceryl trinitrate, erythritol tetranitrate, pentaerythritol tetranitrate, mannitol hexanitrate, perhexilene, isosorbide dinitrate and nicorandil.

10 Beta-adrenergic blocking agents such as alprenolol, atenolol, bupranolol, carteolol, labetalol, metoprolol, nadolol, nadoxolol, oxprenolol, pindolol, propranolol, sotalol, timolol and timolol maleate.

15 Cardiotonic glycosides such as digoxin and other cardiac glycosides and theophylline derivatives.

Adrenergic stimulants such as adrenaline, ephedrine, fenoterol, isoprenaline, 20 orciprenaline, rimiterol, salbutamol, salmeterol, terbutaline, dobutamine, phenylephrine, phenylpropanolamine, pseudoephedrine and dopamine.

Vasodilators such as cyclandelate, isoxsuprime, papaverine, dipyrimadole, isosorbide dinitrate, phentolamine, nicotinyl alcohol, co-dergocrine, nicotinic acid, glyceryl trinitrate, pentaerythritol tetranitrate and xanthinol.

25 Anti-migraine preparations such as ergotamine, dihydroergotamine, methysergide, pizotifen and sumatriptan.

30 Anticoagulants and thrombolytic agents such as warfarin, dicoumarol, low molecular weight heparins such as enoxaparin; streptokinase and its active derivatives. Haemostatic agents such as aprotinin, tranexamic acid and protamine.

Analgesics, antipyretics including the opioid analgesics such as buprenorphine, dextromoramide, dextropropoxyphene, butorphanol, fentanyl, ketamine, alfentanil, sufentanil, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, codeine and 5 dihydrocodeine. Others include acetylsalicylic acid (aspirin), paracetamol, rizatriptin, sumatriptan, zolmitriptan and phenazone.

Hypnotics and sedatives such as the barbiturates, amylobarbitone, butobarbitone and pentobarbitone and other hypnotics and sedatives such as 10 ketamine, choral hydrate, chlormethiazole, hydroxyzine and meprobamate.

Anti-anxiety agents such as the benzodiazepines, alprazolam, bromazepam, chlordiazepoxide, clobazam, chlorazepate, diazepam, flunitrazepam, flurazepam, lorazepam, nitrazepam, buspirone, oxazepam, temazepam and 15 triazolam.

Neuroleptic and antipsychotic drugs such as the phenothiazines, chloropromazine, fluphenazine, pericyazine, perphenazine, promazine, thiopropazate, thioridazine and trifluoperazine and the butyrophenones, 20 droperidol and haloperidol and the other antipsychotic drugs such as pimozide, thiothixene, olanzapine and lithium.

Antidepressants such as the tricyclic antidepressants amitryptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, nortriptyline, 25 opipramol, protriptyline and trimipramine and the tetracyclic antidepressants such as mianserin and the monoamine oxidase inhibitors such as isocarboxazid, phenelizine, tranylcypromine and moclobemide and selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, citalopram, fluvoxamine and sertraline.

30

CNS stimulants such as caffeine and methyl phenidate.

Anti-Alzheimer's agents such as tacrine, zinc chelators such as phenanthrolines and their derivatives, such as 1,10 phenanthroline, aryl propionic acids and their derivatives, such as ibuprofen and flurbiprofen.

- 5 Anti-Parkinson agents such as apomorphine, amantadine, benserazide, carbidopa, rivastigmine, levodopa, benzotropine, biperiden, benzhexol, procyclidine, pergolide, ropinirole and dopamine-2 agonists such as S(-)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin (N-0923).
- 10 Anticonvulsants such as phenytoin, valproic acid, primidone, phenobarbitone, methylphenobarbitone and carbamazepine, ethosuximide, methsuximide, phensuximide, sulthiame and clonazepam.
- 15 Antiemetics, antinauseants such as the phenothiazines, prochlorperazine, thiethylperazine and 5HT-3 receptor antagonists such as ondansetron, tropisetron and granisetron and others such as dimenhydrinate, diphenhydramine, metoclopramide, domperidone, hyoscine, hyoscine hydrobromide, hyoscine hydrochloride, clebopride and brompride.
- 20 Non-steroidal anti-inflammatory agents including their racemic mixtures or individual enantiomers where applicable, such as ibuprofen, flurbiprofen, ketoprofen, aclofenac, diclofenac, alopiprin, aroxen, aspirin, diflunisal, fenoprofen, indomethacin, mefenamic acid, naproxen, phenylbutazone, piroxicam, salicylamide, salicylic acid, sulindac, desoxysulindac, tenoxicam,
- 25 tramadol and ketorolac, salicylamide, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, coichicine, demecolcine, allopurinol, oxypurinol, benzylamine hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranyline hydrochloride,
- 30 tetrydamine, benzindopyrine hydrochloride, fluprofen, ibufenac, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole, neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, and triflumidate.

Anti-rheumatoid agents such as penicillamine, aurothioglucose, sodium aurothiomalate, methotrexate and auranofin.

5 Muscle relaxants such as baclofen, diazepam, cyclobenzaprine hydrochloride, dantrolene, methocarbamol, orphenadrine and quinine.

Agents used in gout and hyperuricaemia such as allopurinol, colchicine, probenecid and sulphapyrazone.

10

Oestrogens such as oestradiol, oestriol, oestrone, ethynodiol, mestranol, stilboestrol, dienoestrol, epioestriol, estropipate and zeronol.

15 Progesterone and other progestagens such as allyloestrenol, dydrogesterone, lynoestrenol, norgestrel, norethynodrel, norethisterone, norethisterone acetate, gestodene, levonorgestrel, medroxyprogesterone and megestrol.

Antiandrogens such as cyproterone acetate, flutamide and danazol.

20 Anti-oestrogens such as tamoxifen and epitiostanol and the aromatase inhibitors, exemestane and 4-hydroxy-androstenedione and its derivatives.

25 Androgens and anabolic agents such as calusterone, clostebol acetate, dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), dromostanolone propionate, drostanolone, enanthate, ethylestrenol, fluoxymesterone, furazabol, methandriol, methandrostenolone, methyltestosterone, nandrolone decanoate, nandrolone oxandrolone, oxymetholone, nandrolone phenpropionate, stanozolol, testolactone, testosterone, testosterone cypionate, testosterone propionate, testosterone 30 trenbolone acetate, 7-methyl-19-testosterone (MENT), and 17- α -methyl-19-nortestosterone.

Anti-alopecia agents such as minoxidil, cromakalin, pinacidil, naminidil, diphenylcyclopropenone, tricomin, and those compounds selected from the classes of s-triazines, benzopyrans, pyridinopyrans and thiane-1-oxides.

5 5-alpha reductase inhibitors such as finasteride, turosteride, LY-191704, MK-386 and dutasteride.

10 Corticosteroids such as betamethasone, betamethasone valerate, cortisone, dexamethasone, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, fluocinonide desonide, fluocinolone, fluocinolone acetonide, fluocortolone, halcinonide, halopredone, hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate methylprednisolone, prednisolone, prednisolone 21-phosphate, prednisone, triamcinolone, triamcinolone acetonide.

15 15 Further examples of steroidal anti-inflammatory agents include cortodoxone, fluoracetonide, fludrocortisone, difluorsone diacetate, flurandrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and its other esters, chloroprednisone, clorcortelone, descinolone, desonide, dichlorisone, difluprednate, flucetonide, flumethasone, flunisolide, flucortolone, fluoromethalone, fluperolone, fluprednisolone, meprednisone, methylmeprednisolone, paramethasone, cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone, betamethasone benzoate, chloroprednisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucetonide, flumethasone pivalate, flunisolide acetate, fluperolone acetate, fluprednisolone valerate, paramethasone acetate, prednisolamate, prednival, triamcinolone hexacetonide, cortivazol, formocortal and nivazol.

30 Pituitary hormones and their active derivatives or analogues such as corticotrophin, thyrotropin, follicle stimulating hormone (FSH), luteinising hormone (LH) and gonadotrophin releasing hormone (GnRH).

Hypoglycaemic agents such as insulin, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide and metformin.

5 Thyroid hormones such as calcitonin, thyroxine and liothyronine and antithyroid agents such as carbimazole and propylthiouracil.

Other miscellaneous hormone agents such as octreotide.

10 Pituitary inhibitors such as bromocriptine.

Ovulation inducers such as clomiphene.

15 Anti-muscarinic agents including atropine, belladonna alkaloids, benzatropine (benztropine), biperiden, cyclopentolate, dicycloverine (dicyclomine), flavoxate, homatropine, hyoscine, ipratropium, orphenadrine, oxitropium, oxybutynin, procyclidine, propantheline, propiverine, tiotropium, tolterodine, trihexyphenidyl (benzhexol), tropicamide and trospium.

20 Diuretics such as the thiazides, related diuretics and loop diuretics, bendrofluazide, chlorothiazide, chlorthalidone, dopamine, cyclopenthiazide, hydrochlorothiazide, indapamide, mefruside, methycholthiazide, metolazone, quinethazone, bumetanide, ethacrynic acid and frusemide and potassium sparing diuretics, spironolactone, amiloride and triamterene.

25 Antidiuretics such as desmopressin, lypressin and vasopressin including their active derivatives or analogues.

Obstetric drugs including agents acting on the uterus such as ergometrine, oxytocin and gemeprost.

30 Prostaglandins such as alprostadil (PGE1), prostacyclin (PGI2), dinoprost (prostaglandin F2-alpha) and misoprostol.

Antimicrobials including the cephalosporins such as cephalexin, cefoxytin and cephalothin.

5 Penicillins such as amoxicillin, amoxicillin with clavulanic acid, ampicillin, bacampicillin, benzathine penicillin, benzylpenicillin, carbenicillin, cloxacillin, methicillin, phenethicillin, phenoxyethylpenicillin, flucloxacillin, mezlocillin, piperacillin, ticarcillin and azlocillin.

10 Tetracyclines such as minocycline, chlortetracycline, tetracycline, demeclocycline, doxycycline, methacycline and oxytetracycline and other tetracycline type antibiotics.

Aminoglycosides such as amikacin, gentamicin, kanamycin, neomycin, netilmicin and tobramycin.

15 Antifungals such as butenafine, butoconazole, clioquinol, itraconazole, lanoconazole, neticonazole, tioconazole, terconazole, ciclopirox olamine, amorolfine, isoconazole, clotrimazole, econazole, miconazole, nystatin, terbinafine, bifonazole, amphotericin, griseofulvin, ketoconazole, fluconazole and flucytosine, salicylic acid, fezatione, tiplatone, tolnaftate, triacetin, zinc, pyrithione and sodium pyrithione.

20 Quinolones such as nalidixic acid, cinoxacin, ciprofloxacin, enoxacin and norfloxacin.

25 Sulphonamides such as phthalylsulphthiazole, sulfadoxine, sulphadiazine, sulphamethizole and sulphamethoxazole.

Sulphones such as dapsone.

30 Other miscellaneous antibiotics such as chloramphenicol, clindamycin, erythromycin, erythromycin ethyl carbonate, erythromycin estolate, erythromycin glucepate, erythromycin ethylsuccinate, erythromycin lactobionate, roxithromycin, lincomycin, natamycin, nitrofurantoin,

spectinomycin, vancomycin, aztreonam, colistin IV, metronidazole, tinidazole, fusidic acid and trimethoprim; 2-thiopyridine N-oxide; halogen compounds, particularly iodine and iodine compounds such as iodine PVP complex and diiodohydroxyquin; hexachlorophene; chlorhexidine; chloroamine compounds;

5 benzoylperoxide.

Anti-tuberculosis drugs such as ethambutol, isoniazid, pyrazinamide, rifampicin and clofazimine.

10 Antimalarials such as primaquine, pyrimethamine, chloroquine, hydroxychloroquine, quinine, mefloquine and halofantrine.

15 Antiviral agents such as acyclovir and acyclovir prodrugs, famciclovir, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, saquinavir, indinavir, ritonavir, n-docosanol, tromantadine and idoxuridine.

Anthelmintics such as mebendazole, thiabendazole, niclosamide, praziquantel, pyrantel embonate and diethylcarbamazine.

20 Cytotoxic agents such as plicamycin, cyclophosphamide, dacarbazine, fluorouracil and its prodrugs, methotrexate, procarbazine, 6-mercaptopurine and mucophenolic acid.

25 Anorectic and weight reducing agents including dexfenfluramine, fenfluramine, diethylpropion, mazindol and phentermine.

Agents used in hypercalcaemia such as calcitriol, dihydrotachysterol and their active derivatives or analogues.

30 Antitussives such as ethylmorphine, dextromethorphan and pholcodine.

Expectorants such as acetylcysteine, bromhexine, emetine, guaiphenesin, ipecacuanha and saponins.

Decongestants such as phenylephrine, phenylpropanolamine and pseudoephedrine.

5 Bronchospasm relaxants such as ephedrine, fenoterol, orciprenaline, rimiterol, salbutamol, sodium cromoglycate, cromoglycic acid and its prodrugs, terbutaline, ipratropium bromide, salmeterol and theophylline and theophylline derivatives.

10 Antihistamines such as meclozine, cyclizine, chlorcyclizine, hydroxyzine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, diphenhydramine, diphenylamine, doxylamine, mebhydrolin, pheniramine, tripolidine, azatadine, diphenylpyraline, methdilazine, terfenadine, astemizole, loratadine and cetirizine.

15 Local anaesthetics such as bupivacaine, amethocaine, lignocaine, cinchocaine, dibucaine, mepivacaine, prilocaine and etidocaine.

Neuromuscular blocking agents such as suxamethonium, alcuronium, pancuronium, atracurium, gallamine, tubocurarine and vecuronium.

20 Smoking cessation agents such as nicotine, bupropion and ibogaine.

Insecticides and other pesticides which are suitable for local or systemic application.

25 Dermatological agents, such as vitamins A and E, vitamin E acetate and vitamin E sorbate.

Nutritional agents, such as vitamins, essential amino acids and essential fats.

30 Keratolytics such as the alpha-hydroxy acids, glycolic acid and salicylic acid.

Psychic-energisers, such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

Anti-acne agents such as containing isotretinoin, tretinoin and benzoyl peroxide.

Anti-psoriasis agents such as containing etretinate, cyclosporin and calcipotriol.

5

Anti-itch agents such as capsaicin and its derivatives such as nonivamide [Tsai, et al. Drug. Dev. Ind. Pharm., 20(4), 719, 1994].

10

Anticholinergic agents, which are effective for the inhibition of axillary sweating and for the control of prickly heat. The antiperspirant activity of agents such as methatropine nitrate, propantheline bromide, scopolamine, methscopolamine bromide, and the new class of soft antiperspirants, quaternary acyloxymethyl ammonium salts.

15

Other physiologically active peptides and proteins, small to medium sized peptides, e.g., vasopressin and human growth hormone.

20

The membrane may comprise one or more solvent reservoirs. The portion of membrane between the reservoir and the adhesive layer may be a one-way membrane. The one way membrane may function so that drug extracted from the systemic circulation and/or skin layers permeates through the one-way membrane and into the solvent reservoir.

25

The membrane is preferably administered to the application site within 4 days of transdermal drug application, more preferably within 24 hours of transdermal drug application, and most preferably within 1 hour of transdermal drug application.

30

Preferred aspects of the invention are described in more detail with reference to the attached drawings.

In the accompanying drawings:

Figure 1 is a schematic drawing showing a cross section of an occlusive membrane which has been applied to a topically treated area of skin in accordance with a preferred embodiment of the present invention.

Figure 2 is a schematic drawing showing a cross section of an occlusive membrane applied to a topically treated area of skin in accordance with an alternative, though less preferred, embodiment of the invention

Figure 3 is a graph showing the mean (\pm SEM; n=5) serum concentration-time profiles after application of treatment A (a single dose of 140 μ l fentanyl formulation) or treatment B (a single dose of 140 μ l fentanyl formulation followed by occlusion for 24 hours). Values below the assay LOQ (0.1 ng/ml) have been omitted;

Figure 4 is a graph showing the cumulative amount of testosterone diffused across skin with and without solvent reservoir membrane application;

Referring to the drawings Figure 1 shows a membrane assembly (1) in accordance with a preferred embodiment of the invention comprising an occlusive membrane (2) having a skin side surface (3) to be applied adjacent an area of topically treated skin(4) and a free surface(5) remote there from. The skin side surface (3) is provided with an adhesive layer (6) formed of a suitable skin safe adhesive.

In the method of the invention the membrane assembly (1) is used in circumstances where it is necessary to terminate or reduce transdermal administration following topical application of the active in a transdermal formulation. The need to terminate or reduce transdermal administration may arise as a result of learning after the event that an overdose has been topically applied or the occurrence of adverse reaction or other any other factor which may lead to it being considered desirable to reduce the dose which would otherwise result from the initial topical application. The area of topical application (4) is identified and the membrane assembly applied preferably with sufficient dimensions to at least substantially cover the area of topical application (4). The membrane assembly (1) is applied to the skin in the area of application (4) so that the adhesive layer (6) on the skin contacting side (3) of

the membrane (3) makes adhering contact with the skin (4). Pressure, such as firm hand pressure, is preferably applied to the free surface (5) of the occlusive membrane (2) to urge the membrane assembly (1) into a uniformly adhering contact with the skin (4).

5

Referring to Figure 2 the alternative membrane assembly (7) comprises a multilayer semi permeable membrane (8) comprising a skin side layer (9) which is selectively permeable to allow the ingress of the topically applied composition. The skin side layer (9) is provided with a skin contacting adhesive (10) on the skin side thereof (11) and is bonded to a second layer (12), which may be impermeable, on the remote side (13). One or more reservoirs of solvent (14) are provided between the first (9) and second layers (12). The solvent reservoir (14) may provide an osmotic potential promoting absorption of topical composition through the first (selectively permeable) layer (9). Preferably the first membrane layer (9) is substantially impermeable to the egress of solvent from the solvent reservoir (14). In this embodiment the method of the invention includes applying the membrane assembly to the area of skin to which the topical application has occurred (15). The assembly (7) is applied so that the adhesive layer (10) is brought into adhering contact with the skin (15) and the adhesion is preferably made substantially uniform by application of pressure (e.g. hand pressure) to the outer side (18) of the membrane assembly.

20

The choice of solvent used in the reservoir may be selected on the basis of the particular drug previously administered in order to achieve the desired extraction effect, since the drug must be at least partially soluble in the selected solvent. Preferably, the solvent is an alcohol, alkane, ether, ketone, chlorinated hydrocarbon or nitrile. More preferably the solvent is aliphatic C₁-C₄. Most preferably the solvent is selected from the group consisting of ethanol and its derivatives, methanol, chloroform, isopropyl alcohol or a mixture of two or more of the aforementioned solvents.

25

The amount of solvent used will depend on the period which has elapsed following initial topical application and the physico chemical properties of the solvent and drug and the area of application of the drug.

30

The occlusive or semi-permeable membrane is applied to the transdermal application site preferably within 4 days, more preferably within 24 hours and most preferably within 1 hour.

5

The occlusive or semi-permeable membrane is applied to as much of the transdermal drug application site as possible, including the surrounding area and remains in place preferably for 12 hours, more preferably for 24 hours.

10 Conveniently, the occlusive or semi-permeable membrane is coated with a layer of an adhesive, to achieve a fixed and secure positioning on the skin.

In a further embodiment the invention provides for a method of solvent extraction whereby the drug application site may be swabbed with a solvent mix 15 and/or the occlusive or semi-permeable membrane contains a reservoir solvent. In a particularly preferred form of the invention the solvent is a lower alcohol, more preferably methanol or chloroform, or a mixture thereof.

20 The amount of drug prevented from absorption and/or extracted will depend on a number of factors and will vary from subject to subject and depend on the particular drug administered and the length of time prior to application of the occlusive or semi-permeable membrane. The desired effect of the present invention is such that the quantity of drug present will not exceed a rate of release that reaches levels that provide the undesired effect.

25

The invention will now be described with reference to the following examples. It is to be understood that the examples are provided by way of illustration of the invention and that they are in no way limiting to the scope of the invention.

30 **Example 1**

The objectives of this pharmacokinetic study were to determine the pharmacokinetics of fentanyl after single dosing in healthy volunteers and to compare the pharmacokinetic profile of the fentanyl profile with and without occlusion of the application site.

Method

The study was a parallel design. In the first stage 5 healthy volunteers received treatment A. The second stage 5 healthy volunteers received treatment B. The 5 treatments consisted of a single application of 140 μ l fentanyl formulation applied to the abdomen, with and without occlusion of the application site. Serum fentanyl concentration profiles were measured over 72 hours after administration of transdermal fentanyl. A validated GC/MS assay was used to analyse fentanyl concentrations in the serum samples.

10

Study Treatments

Treatment A: Fentanyl formulation (140 μ l) containing 7.5% fentanyl and 5.0% Octisalate applied to the lateral abdomen.

Treatment B: Fentanyl formulation (140 μ l) containing 7.5% fentanyl and 5.0% Octisalate applied to the lateral abdomen and then covered by an occlusive dressing to the whole area within 2 minutes (polyurethane membrane coated with a layer of an acrylic adhesive) for 24 hours.

Result

Treatment B (fentanyl formulation with occlusion) produced very low levels of serum fentanyl (Figure 3). Values below the assay LOQ (0.1 ng/ml) have been omitted from the graphs. The values were significantly lower than the levels seen after application of Treatment A (fentanyl formulation without occlusion). This indicates that occlusion of the application site with polyurethane membrane patches, coated with a layer of an acrylic adhesive, significantly reduces absorption from the skin reservoir.

Table 1: Mean (\pm S.E.M.) pharmacokinetic parameters following application of treatments A and B.

| Treatment | AUC_{0-72h} (ng/mL.h) | C_{max} (ng/mL) | t_{max} (hours) |
|-----------|----------------------------|----------------------|----------------------|
|-----------|----------------------------|----------------------|----------------------|

| | | | |
|-----------------------|--------------|-------------|-----------|
| A (without occlusion) | 11.89 ± 7.00 | 0.33 ± 0.21 | 36 ± 9.12 |
| B (with occlusion) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0 ± 0.00 |

Example 2

The occlusive or semi-permeable membrane may contain a reservoir solvent.

The choice of solvent used in the reservoir may be selected on the basis of the 5 particular drug previously administered in order to achieve the desired extraction effect. The aforementioned examples are not meant to be limiting and it is envisaged that combinations of solvents could also be used to obtain the desired pharmacological effect, for example on a weight basis

| Solvent | Ratio (%w/w) |
|-----------------------|---------------|
| Methanol : Chloroform | 20-80 : 20-80 |

10

Figure 4 depicts the in-vitro diffusion profile that may be obtained by application of a solvent reservoir membrane immediately following undesirable administration of testosterone.

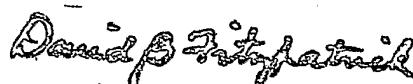
15 Finally, it is understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

DATED: 10 December, 2003

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Attorneys for:

ACRUX DDS PTY LTD



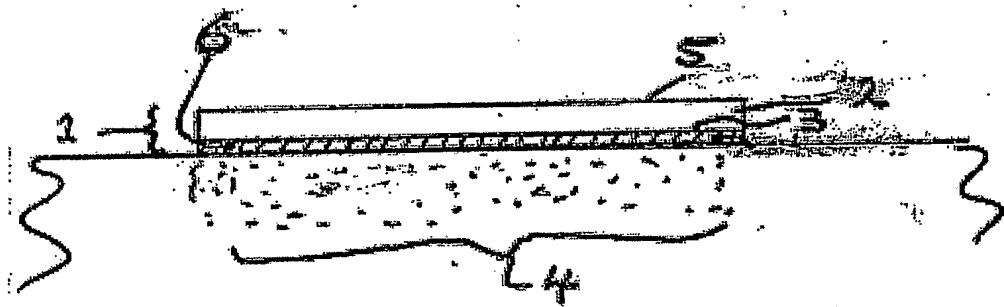


FIGURE 1

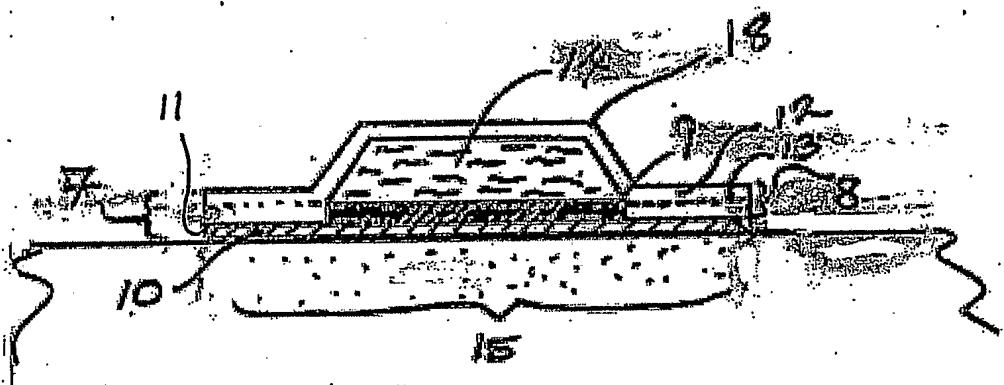


FIGURE 2

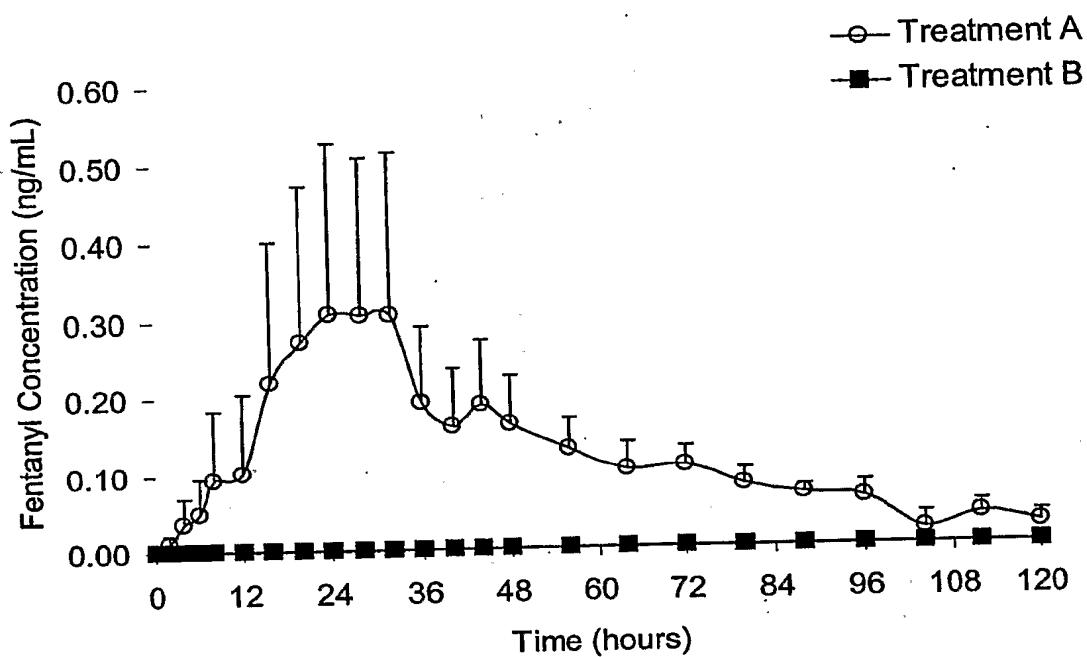


FIGURE 3

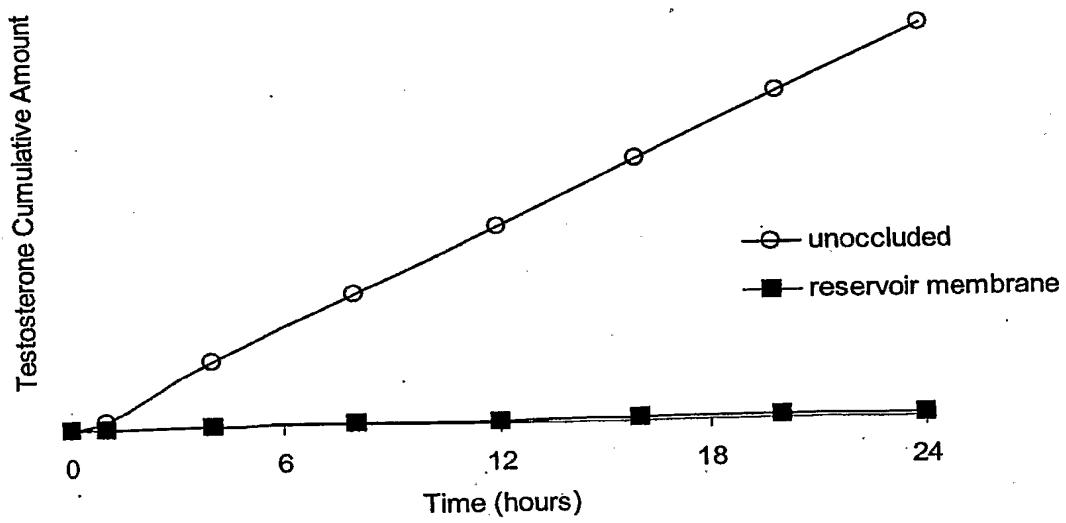


FIGURE 4